(19) Europäis hes Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 113 570**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 83307692.0

(22) Date of filing: 16.12.83

(51) Int. Cl.³: C 07 D 233/88
C 07 D 233/60, C 07 D 401/04
C 07 D 401/06, A 61 K 31/415

(30) Priority: 20.12.82 US 450848

(43) Date of publication of application:
18.07.84 Bulletin 84/29

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: MERCK & CO. INC.
126, East Lincoln Avenue P.O. Box 2000
Rahway New Jersey 07065(US)

(72) Inventor: Chabala, John C.
560 Sherwood Parkway
Westfield New Jersey 07090(US)

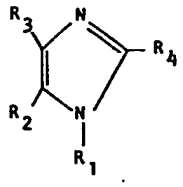
(72) Inventor: Fisher, Michael H.
R.D. 1, Old York Road
Ringoes New Jersey 08551(US)

(72) Inventor: Patchett, Arthur A.
1090 Minisink Way
Westfield New Jersey 07090(US)

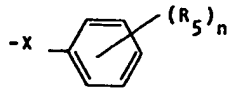
(74) Representative: Crampton, Keith John Allen et al,
D YOUNG & CO 10 Staple Inn
London WC1V 7RD(GB)

(54) 5-(Amino or substituted amino) imidazoles.

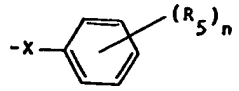
(57) 5-(Amino or substituted amino) imidazoles of the formula:



in which R_1 is (a) mono-substituted phenyl or mono-substituted phenalkyl where the substituent is trifluoromethyl, C_{2-3} alkanoyl, nitro, carboxy, alkoxycarbonyl, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl or



where n is from 1 to 5, R_5 is as defined below and X is O, S, SO, SO_2, CH_2, CO, CHOH, CHCN or $C{=}NR_6$ where R_6 is hydrogen, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-3} alkylamino, or di(C_{1-3} alkyl)amino; (b) phenyl or phenalkyl having from two to five R_5 substituents where each R_5, independently of the other(s), is halogen, cyano, trifluoromethyl, C_{2-3} alkanoyl, nitro, C_{1-3} alkyl, C_{1-3} alkoxy, carboxy, alkoxycarbonyl, trifluoromethoxy, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or



where R_5, X, and n are as defined above, provided that if the monosubstituent or one of the polysubstituents is halogen, C_{1-3} alkyl or C_{1-3} alkoxy, such atoms or groups are in positions other than those *ortho* to the positions of attachment of the phenyl to the imidazole or the alkyl that is in turn attached to the imidazole: or (c) phenacyl, pyridyl, pyridylmethyl, naphthyl, naphthylmethyl, quinolyl, or quinolylmethyl;

R_2 is amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, acetamido, acetimido, ureido, formamido, formimido or guanidino;

R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; and

./...

EP 0 113 570 A1

R_4 is hydrogen, C_{1-3} alkyl, hydroxy, amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, phenyl, cyano, C_{1-3} alkoxy, C_{2-3} alkanoyloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or C_{1-3} alkylsulfonyl are novel and possess anticoccidial activity. The compounds are useful for controlling caecal and or intestinal coccidiosis when administered in minor quantities to animals, in particular to poultry, usually in admixture with animal sustenance.

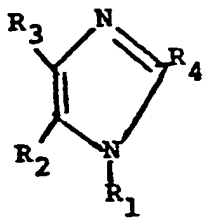
5-(AMINO OR SUBSTITUTED AMINO) IMIDAZOLES

This invention relates to anticoccidial compounds and their preparation.

Coccidiosis is a widespread poultry disease produced by infections of protozoa of the genus Eimeria, which causes severe pathology in the intestines and caeca of poultry. Some of the most significant of these species are E. tenella, E. acervulina, E. necatrix, E. brunetti, E. maxima, E. mitis, E. mivati, E. hagani and E. praecox. The disease is generally spread by the birds picking up the infectious organism in droppings on contaminated litter or ground or by way of food or drinking water. The disease is manifested by haemorrhage, accumulation of blood in the caeca, passage of blood to the droppings, weakness and digestive disturbances. The disease often terminates in death but the market value of fowl that survive severe infections is substantially reduced as a result. Coccidiosis is therefore a disease of great economic importance and extensive work has been done to find new and improved methods for controlling and treating coccidial infections in poultry.

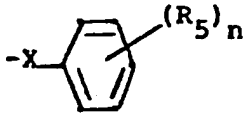
This invention is based on the discovery that certain novel 5-amino and substituted amino imidazoles and certain of their substituted derivatives have a surprisingly and unexpectedly high degree of activity against coccidiosis of poultry.

The present invention provides a compound having the formula:



in which R_1 is (a) mono-substituted phenyl or mono-substituted phenalkyl where the substituent is trifluoromethyl, C_{2-3} alkanoyl, nitro, carboxy, alkoxycarbonyl, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl or

where n is from 1 to 5, R_5 is as defined below and X is O, S, SO, SO_2, CH_2, CO, CHOH, CHCN or $C{=}NR_6$ where R_6 is hydrogen, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-3} alkylamino, or di(C_{1-3} alkyl)amino; (b) phenyl or phenalkyl having from two to five R_5 substituents where each R_5, independently of the other(s), is halogen, cyano, trifluoromethyl, C_{2-3} alkanoyl, nitro, C_{1-3} alkyl, C_{1-3} alkoxy, carboxy, alkoxycarbonyl, trifluoromethoxy, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or



where R_5, X, and n are as defined above, provided that if the monosubstituent or one of the polysubstituents is halogen, C_{1-3} alkyl or C_{1-3} alkoxy, such atoms or groups are in positions other than those ortho to the positions of attachment of the phenyl to the imidazole or the alkyl that is in turn attached to the imidazole; or (c) phenacyl, pyridyl, pyridylmethyl, naphthyl, naphthylmethyl, quinolyl, or quinolylmethyl;

R_2 is amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, acetamido, acetimido, ureido, formamido, formimido or guanidino;

R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; and

R_4 is hydrogen, C_{1-3} alkyl, hydroxy, amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, phenyl, cyano, C_{1-3} alkoxy, C_{2-3} alkanoyloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or C_{1-3} alkylsulfonyl. Preferably, when a given R_5 is defined so as to include a second R_5 group, then that second R_5 group cannot itself be defined so as to include a third R_5 group.

Administration of a small amount of at least one of the compounds of the invention, preferably in a composition with an inert carrier, conveniently a poultry feed, can be effective in preventing or greatly reducing the incidence of coccidiosis. Such compositions are another aspect of the present invention. The compounds are effective against both the caecal form (caused principally by E. tenella) and the intestinal forms (principally caused by E. acervulina, E. brunetti, E. maxima and E. necatrix). The coccidiostats of this invention are particularly effective against the species that cause caecal damage in addition to preventing the pathology caused by the coccidia. These compounds also exert an inhibitory effect on the oocysts by greatly reducing the number and or the sporulation of those produced. They are administered in compositions that also include an inert carrier.

The compounds of the invention are also active against Eimeria spp, in other animals.

The novel imidazole derivatives of this invention are prepared by reacting an appropriately substituted halide and a 1-unsubstituted imidazole compound in the presence of a base in a suitable reaction medium.

The preferred compounds of the invention are those in which, in the foregoing structural formula, R_1 is monosubstituted phenyl or monosubstituted benzyl where the substituent is a trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl or phenylsulfonyl radical or a halo-substituted, methyl-substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; a di- or trisubstituted phenyl or benzyl radical where the substituents are halogen, cyano, methyl, trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl, phenylsulfonyl, or a halo-substituted, methyl-substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; provided that if the monosubstituent or one of the substituents is halogen, it is ortho to the position of attachment of the phenyl to the imidazole or to the methyl that is in turn attached to the imidazole;

R_2 is amino, lower alkylamino or di(loweralkyl) amino;

R_3 is carbamoyl and

R_4 is hydrogen.

The especially preferred compounds of the invention are those in which R_1 is a phenyl or benzyl radical having 2 or 3 halo, cyano, methyl, trifluoromethyl, halophenoxy, tolyoxy, trifluoromethylphenoxy, halophenylthio, tolylthio, trifluoromethylphenylthio, halophenylsulfinyl, tolysulfinyl, trifluoromethylphenylsulfinyl, halophenylsulfonyl, tolylsulfonyl, trifluoromethylphenylsulfonyl, halobenzoyl, methylbenzoyl, trifluoromethylbenzoyl, halophenyl-hydroxymethyl, methylphenyl-hydroxymethyl and/or trifluoromethylphenyl-hydroxymethyl substituents in the meta and/or para positions;

R_2 is amino;

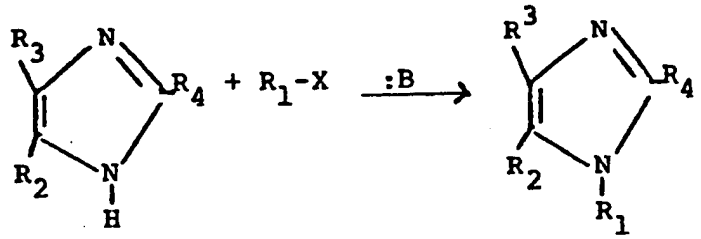
R_3 is carbamoyl; and

R_4 is hydrogen.

In the present specification and claims the term "loweralkyl" means "C_{1-3} alkyl", viz. methyl, ethyl, propyl or isopropyl; the term "loweralkoxy" means "C_{1-3} alkoxy", viz. methoxy, ethoxy, propoxy, or isopropoxy; and the term "lower alkanoyl" means C_{2-3} alkanoyl, viz. acetyl and propionyl.

The compounds of the invention may be prepared by any one of several processes. The most general process is outlined in the following reaction scheme.

Reaction Scheme I

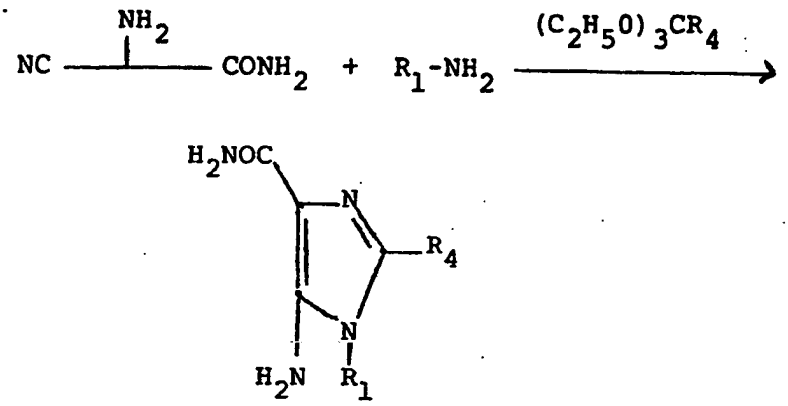


where X is a halogen preferably chlorine or bromine. In the foregoing reaction a 1-unsubstituted but otherwise appropriately substituted imidazole is

reacted with a halogen substituted R_1 group in the presence of a base to prepare the desired 1-substituted imidazole. The reaction is carried out in a solvent which may be any polar aprotic organic solvent such as acetone, dimethylformamide, acetonitrile, dioxane, and the like in the presence of a base. The base may be any non-nucleophilic organic or inorganic base since its purpose is merely to neutralize the acid produced during the course of the reaction. Suitable inorganic bases are alkali metal bases, such as sodium and potassium carbonates, phosphates, bicarbonates and hydroxides. Suitable organic bases are tertiary amines such as trialkyl substituted amines and cyclic aromatic amines such as collidine. The reaction rate varies greatly with the nature of the proposed substituent at the R_1 position, the base being used in the reaction and the solvent. Very reactive substituent and base combinations may be complete in as little as ten minutes and at the other extreme the reaction may take as long as two weeks. Most reactions are however complete in from 1 to 100 hours. The reaction is carried out at a temperature of from room temperature to 100°C or to the reflux temperature of the solvent system being used. The products of the reaction are isolated using techniques known to those skilled in the art.

An alternate procedure for preparing the imidazole compounds wherein R_2 is amino and R_3 is carbamoyl is outlined in the following reaction scheme:

Reaction Scheme 2



wherein R_4 is hydrogen, loweralkyl, or phenyl. The above reaction is carried out in a non-polar aprotic solvent system as described in the preceding reaction scheme. The reaction is carried out by first combining the aminocyanoacetamide and triethylorthoformate in the solvent and stirring at from room temperature to 100°C or to the reflux temperature of the solvent system being employed for from 10 minutes to 3 hours. Generally this phase of the reaction is complete in from 1/2 to 1 hour. However, following this reaction period the R_1 substituted amine is added to the reaction mixture and the reaction stirred for up to 2 hours at from room temperature to 100°C or the reflux temperature of the reaction system. The reaction is oftentimes very fast being evidenced by the immediate production of a precipitate and the product may be isolated immediately. However, generally to insure that the reaction is complete, stirring and heating are continued for a short time. The products of the reaction are isolated using techniques known to those skill d in the art.

The novel compounds of this invention are orally administered to poultry for the control and prevention of coccidiosis. Any number of conventional methods are suitable for administering the coccidiostats of this invention to poultry, as for example, they may be given in the poultry feed. The actual quantity of the coccidiostats administered to the poultry in accordance with this invention will vary over a wide range and be adjusted to individual needs, depending upon species of the coccidia involved and severity of the infection. The limiting criteria are that the minimum amount is sufficient to control coccidiosis and the maximum amount is such that the coccidiostat does not result in any undesirable effects.

A feed typically contains from about 0.0001 to about 0.2 percent, preferably from about 0.001 to about 0.1 percent, by weight of one of the coccidiostats of this invention. The optimum levels will naturally vary with the specific compound utilized and species of Eimeria involved, and can be readily determined by one skilled in the art. Levels of the 5-amino and substituted amino imidazoles of this invention, in poultry feed of from about 0.001 percent to about 0.1 percent by weight of the diet are especially useful in controlling the pathology associated with E. tenella, as well as the intestinal dwelling species.

Depending on the compound employed, levels of 0.001 percent to 0.006 percent possess the novel effects of reducing the number of oocysts passed in the droppings of infected chickens and/or inhibiting the subsequent division and maturation to infectivity,

scientifically designated as the process of sporulation. Thus, the combination of prevention of pathology, coupled with the inhibiting effect on the reproductive product of these organisms, the oocysts, present a unique two-fold method for the control of coccidiosis in poultry.

The quantity or concentration of a novel coccidiostat of this invention in any admixture in which it is administered to the poultry will, of course, vary in accordance with the type of admixture utilized.

Of the various methods of administering the coccidiostats of this invention to poultry, they are most conveniently administered as a component of a feed composition. The novel coccidiostats may be readily dispersed by mechanically mixing the same in finely ground form with the poultry feedstuff, or with an intermediate formulation (premix) that is subsequently blended with other components to prepare the final poultry feedstuff that is fed to the poultry. Typical components of poultry feedstuffs include molasses, fermentation residues, corn meal, ground and rolled oats, wheat shorts and middlings, alfalfa, clover and meat scraps, together with mineral supplements such as bone meal and calcium carbonate and vitamins.

The following non-limiting examples will serve to further illustrate the instant invention.

EXAMPLE 1

Preparation of 1-substituted-5-aminoimidazole-4-carboxamides (Method A)

A mixture of 5-aminoimidazole-4-carboxamide hydrochloride, potassium carbonate, alkyl halide, and

acetone were refluxed together for from 3 to 168 hours, the solvent was concentrated to about 1/6 of the original volume and the mixture filtered. The solid was washed with acetone, slurried in water, and filtered. The remaining solid was slurried in water, treated wth glacial acetic acid to remove residual potassium carbonate, and filtered. The filter cake was washed with water, acetone, and ether to provide the desired 1-substituted-5-aminoimidazole-4-carboxamide. (Table 1).

Table 1

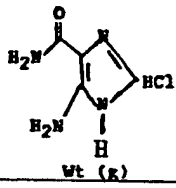
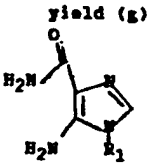
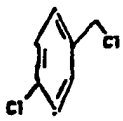
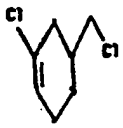
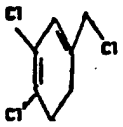
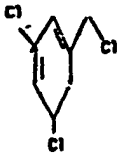
alkyl halide (R_1-X) (X = halogen)	Wt (g)	 Wt (g)	K_2CO_3 Wt (g)	acetone vol (ml)	reflux time (hr)	 yield (g)
	7.25	4.9	16.6	300	48	4.0	271-273[1]
	2.9	1.95	6.6	125	46	1.98	251-252[2]
	8.8	4.9	16.6	300	65	5.15	241-244
	3.5	1.95	6.6	125	64	1.30	247-248[2]

Table 1 (cont'd)

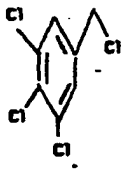
	6.61	3.09	10.5	250	26	2.5	286-287.5[2]
	6.5	4.9	16.6	300	20	5.8	237-241
	7.15	4.9	16.6	300	3	1.2	219-221
	3.5	1.95	6.6	125	48	1.54	192.5-194[2]

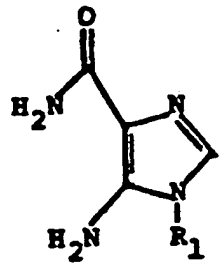
Table 1 (cont'd)

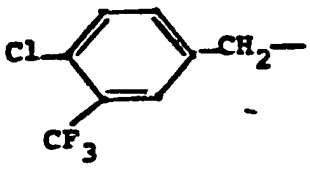
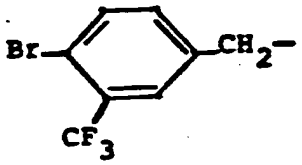
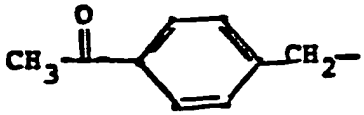
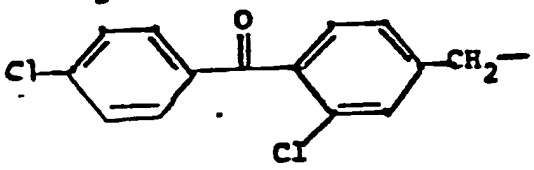
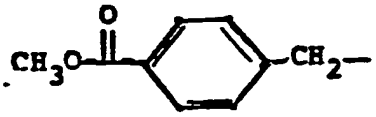
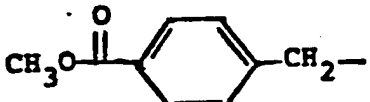
	8.3	4.9	16.6	200	90	1.95	206-209
	6.95	4.9	16.6	200	21	2.9	197-215

1 In this case crude solid product was recrystallized from 65 ml acetic acid-water (10:3 v/v).

2 Melting point after recrystallization from aqueous ethanol.

Other compounds which can be prepared by Method A:



R_1	
	
	
	
	

EXAMPLE 2

Preparation of 1-substituted-5-aminoimidazole-4-carboxamides (Method B)

A mixture of aminocyanoacetamide and triethyl orthoformate in acetonitrile was refluxed for 30-55 minutes. The mixture may be filtered if a small amount of precipitate forms. A primary amine, R_1NH_2, was added and the mixture was refluxed for 15-30 minutes. The mixture was cooled and product collected by filtration (Table 2) or isolated by chromatography.

Table 2

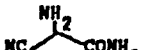
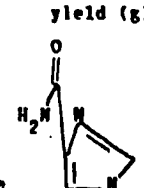
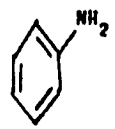
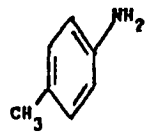
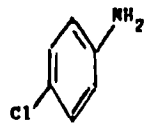
 (g)	$(EtO)_3CH$ (g)	CH_3CN (ml)	reflux time (min.)	amine 	weight amine (g)	additional reflux time (min.)	yield (g) 	melting point (°C)
2.00	3.29	30	45		1.88	15	1.5	190-194
2.00	3.29	30	30		2.16	30	3.1	242.5-254 (dec)
2.00	3.30	30	30		2.58	30	1.7	262-263

Table 2 (cont'd)

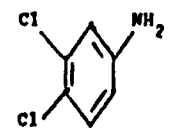
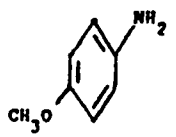
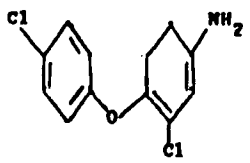
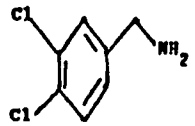
1.48	2.48	22	45		2.40	45	1.97	
2.56	4.21	25	45		3.18	20	3.55	236-238
2.00	3.29	30	45		5.13	15	4.4	188-191[1]
0.297	0.489	4.5	45		0.528	15	0.609	238-240

Table 2 (cont'd)

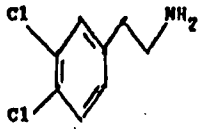
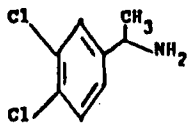
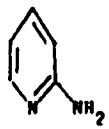
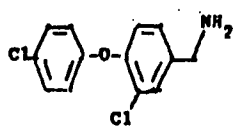
0.531	0.877	8.0	45		1.02	15	0.885	235-237
1.48	2.48	22	45		2.85	15	2.66	247-249
2.00	3.29	30	50		1.92	15	1.05	198.5-200[1]
0.273	0.454	4.1	45		0.751	15	0.340	199-200

Table 2 (cont'd)

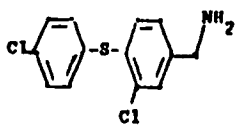
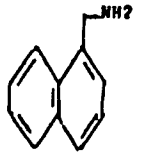
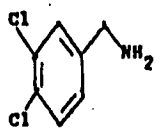
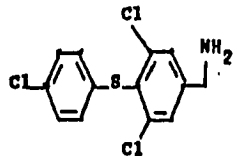
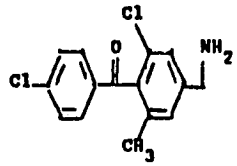
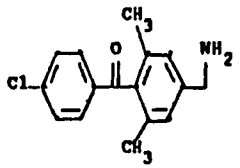
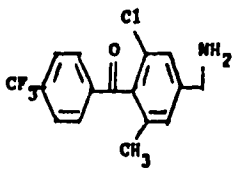
1.24	2.05	18	45		3.6	15	3.16	201-202
0.500	0.820	8.0	45		0.785	15	0.831	258-260
0.870	1.43	14	45		1.38	15	1.62	264-270

Table 2 (cont'd)

0.700	1.25[2]	12	45		1.24	15	1.22[3]	275
0.556	0.89	8.0	45		1.79	15	1.24	221-222
0.314	0.49	4.0	45		0.845	15	0.741	229-230

0113570

Table 2 (cont'd)

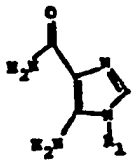
0.332	0.52	4.2	45		0.830	30	0.592	226-227
0.117	0.183	1.5	45		0.350	45	0.121	221-223

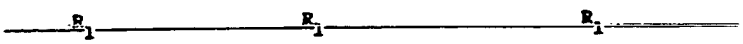
1 Melting point after recrystallization from 98:2 (v/v) ethanol-benzene.

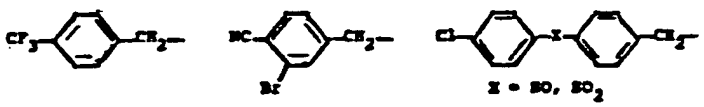
2 Weight of triethylorthoacetate.

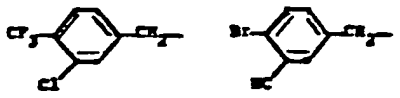
3 Yield of 1-(3,4-dichlorobenzyl)-2-methyl-5-aminoimidazole-4-carboxamide, isolated in two crops, triturated with 20 ml of hot acetonitrile and dried.

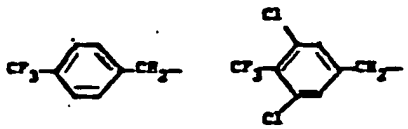
Other compounds which can be prepared by Method B:

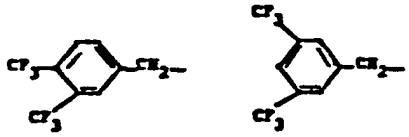


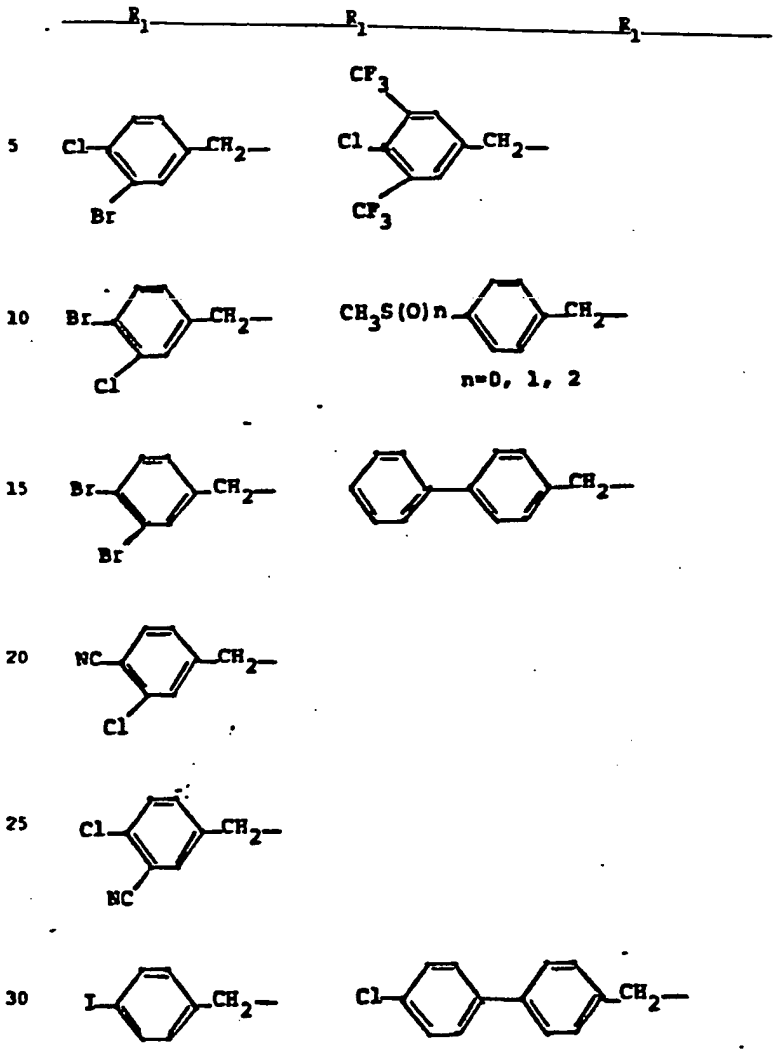











R1
R1
R1
Cl
CH2
Br
CF3
Cl
CH2
CF3
Br
CH2
Cl
CH3S(O)n
CH2
n=0, 1, 2
Br
CH2
Br
CH2
NC
CH2
Cl
Cl
CH2
NC
I
CH2
Cl
CH2

EXAMPLE 3

Preparation of 1-(m-cyanobenzyl)-5-aminoimidazole-4-carboxamide

A mixture of 5-aminoimidazole-4-carboxamide (5.00 g), potassium carbonate (12.0 g), and α-bromo-m-tolunitrile (9.80 g) were refluxed in acetone (300 ml) for 24 hours under a nitrogen atmosphere. The mixture was cooled to room temperature and filtered. The solid residue was washed with acetone and the combined filtrates were evaporated to dryness. The residual solid was dissolved in acetone (50 ml), concentrated to a volume of 20 ml *in vacuo*, and diluted with diethyl ether (100 ml) to provide a gum. The solvent was decanted from the residue and deposited crystals of crude product on standing. The gum was triturated twice with acetone, and the acetone layers were combined with the above crystals, and evaporated to provide 5.9 g of a dark gum. The gum was dissolved in methanol (100 ml), filtered, added to 100 ml. E. Merck 7734 silica gel, and evaporated to dryness *in vacuo*. The product on silica gel was placed on top of a column of 1200 ml E. Merck 7734 silica gel and eluted with 9:1 v/v methylene chloride/methanol. After a forerun of 1.0 l, 400 ml fractions were collected and fractions 8-11 and 12-15 were combined separately and evaporated to dryness. The solid product from fractions 8-11 was triturated with a small volume of acetone and filtered. The filtrate was combined separately with the product from fractions 12-15 and evaporated to dryness. The product was recrystallized from methanol to provide 320 mg of 1-(m-cyanobenzyl)-5-aminoimidazole-4-carboxamide, m.p. 246-247°C.

EXAMPLE 4

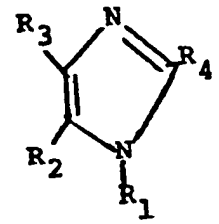
Preparation of 1-(4-chloro-3-trifluoromethylbenzyl)-5-aminoimidazole-4-carboxamide

A mixture of 5-aminoimidazole-4-carboxamide hydrochloride (5.0 g), K_2CO_3 (16.5 g), and a 9:1 w/w mixture of α,4-chloro-3-trifluoromethyltoluene and α,2-dichloro-3-trifluoromethyltoluene were refluxed in acetone (300 ml) for 4 days. Solvent was concentrated in vacuo, the residue was diluted with water, and the solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, 0.5 N acetic acid, and brine, dried, treated with activated charcoal, and filtered. The filtrate was concentrated to provide a first crop of 3.40 g. The filtrate was diluted with ether to provide a second crop of 2.07 g, and the remaining filtrate was diluted with hexane to provide a third crop of 0.25 g. The second and third crops were combined, dissolved in aqueous ethanol, diluted with water, and concentrated to provide 0.97 g of solid. Further concentration of the filtrate provided an additional 0.43 g. The samples weighing 3.40 g, 0.97 g, and 0.43 g were combined, treated with hot 7.5% methanol in ethyl acetate, and diluted with 50 ml ethyl acetate. The resulting solution was chromatographed on a column of 500 ml silica gel, eluted with 7.5% methanol in ethyl acetate followed by 10% methanol in ethyl acetate. A total of 150 fractions of 20 ml each were collected at a flow rate of about 10 ml/min. Fractions 60-118 were combined and evaporated to provide 3.53 g solid. The product was dissolved in 100 ml of boiling ethanol, treated

with activated charcoal, and filtered. The filtrate was concentrated to provide a first crop of crystals, and further concentration of the filtrate provided a second crop. The two crops were combined and recrystallized from 50 ml of ethanol to provide 1.99 g 1-(4-chloro-3-trifluoromethylbenzyl)-5-amino-imidazole-4-carboxamide, m.p. 230.5-232.5°C.

CLAIMS

1. A compound having the formula:



in which R_1 is (a) mono-substituted phenyl or mono-substituted phenalkyl where the substituent is trifluoromethyl, C_{2-3} alkanoyl, nitro, carboxy, alkoxycarbonyl, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl or

where n is from 1 to 5, R_5 is as defined below and X is O, S, SO, SO_2, CH_2, CO, CHOH, CHCN or $C{=}NR_6$ where R_6 is hydrogen, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-3} alkylamino, or di(C_{1-3} alkyl)amino; (b) phenyl or phenalkyl having from two to five R_5 substituents where each R_5, independently of the other(s), is halogen, cyano, trifluoromethyl, C_{2-3} alkanoyl, nitro, C_{1-3} alkyl, C_{1-3} alkoxy, carboxy, alkoxycarbonyl, trifluoromethoxy, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or

where R_5, X, and n are as defined above, provided that if the monosubstituent or one of the polysubstituents is halogen, C_{1-3} alkyl or

C_{1-3} alkoxy, such atoms or groups are in positions other than those ortho to the positions of attachment of the phenyl to the imidazole or the alkyl that is in turn attached to the imidazole; or (c) phenacyl, pyridyl, pyridylmethyl, naphthyl, naphthylmethyl, quinolyl, or quinolylmethyl;

R_3 is amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, acetamido, acetimido, ureido, formamido, formimido or guanidino;

R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; and

R_4 is hydrogen, C_{1-3} alkyl, hydroxy, amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, phenyl, cyano, C_{1-3} alkoxy, C_{2-3} alkanoyloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or C_{1-3} alkylsulfonyl.

2. A compound as claimed in Claim 1, in which R_1 is monosubstituted phenyl or monosubstituted benzyl where the substituent is a trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl or phenylsulfonyl radical or a halo-substituted, methyl-substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; a di- or trisubstituted phenyl or benzyl radical where the substituents are halogen, cyano, methyl, trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl, phenylsulfonyl, or a halo-substituted, methyl-substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; provided that if the monosubstituent or one of the substituents is halogen, it is ortho to the position of attachment of the phenyl to the imidazole or to the methyl that is in turn attached to the imidazole;

R_2 is amino, C_{1-3} alkylamino or di(C_{1-3} alkyl)amino;

R_3 is carbamoyl and

R_4 is hydrogen.

3. A compound as claimed in Claim 2, in which R_1 is a phenyl or benzyl radical having 2 or 3 halo, cyano, methyl, trifluoromethyl, halophenoxy,

tolyoxy, trifluoromethylphenoxy, halophenylthio, tolylthio, trifluoromethylphenylthio, halophenylsulfinyl, tolysulfinyl, trifluoromethylphenylsulfinyl, halophenylsulfonyl, tolylsulfonyl, trifluoromethylphenylsulfonyl, halobenzoyl, methylbenzoyl, trifluoromethylbenzoyl, halophenyl-hydroxymethyl, methylphenyl-hydroxymethyl and/or trifluoromethylphenyl-hydroxymethyl substituents in the meta and/or para positions;

R_2 is amino;

R_3 is carbamoyl; and

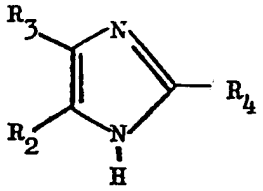
R_4 is hydrogen.

4. 5-Amino-1-(3,4,5-trichlorobenzyl)imidazole-4-carboxamide.

5. 5-Amino-1-[4-(4-chlorophenylthio)-3-chlorobenzyl] imidazole-4-carboxamide.

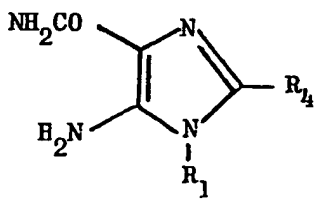
6. 5-Amino-1-[4-(4-chlorophenoxy)-3-chlorobenzyl] imidazole-4-carboxamide.

7. A process for the preparation of a compound as claimed in Claim 1 comprising reacting a compound having the formula



with an R_1-substituted halide in the presence of a base to produce the desired compound, R_1, R_2, R_3 and R_4 being as defined in Claim 1.

8. A process for the preparation of a compound as claimed in Claim 1 and having the formula



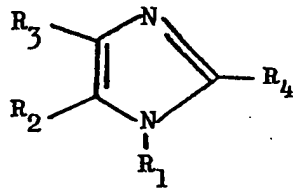
comprising treating aminocyanoacetamide with an R_1-substituted amine in the presence of a compound of formula $(C_2H_5O)_3CR_6$ to produce the desired compound, R_6 being hydrogen, C_{1-3} alkyl, or phenyl and R_1 and R_4 being as defined in Claim 1.

9. A compound as claimed in any one of Claims 1 to 6 for use in administration to an animal for the purpose of preventing or treating coccidiosis.

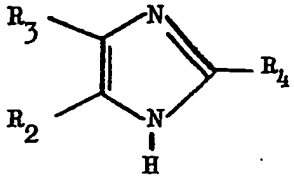
10. A composition useful for the prevention and treatment of coccidiosis which comprises an inert carrier and a compound as claimed in any one of Claims 1 to 6.

CLAIMS FOR AUSTRIA

1. A process for preparing a compound of formula



comprising reacting a compound having the formula



with an R_1-substituted halide in the presence of a base to produce the desired compound, where in the formula, R_1 is (a) mono-substituted phenyl or mono-substituted phenalkyl where the substituent is trifluoromethyl, C_{2-3} alkanoyl, nitro, carboxy, alkoxycarbonyl, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl or

where n is from 1 to 5, R_5 is as defined below and X is O, S, SO, SO_2, CH_2, CO, CHOH, CHCN or $C{=}NR_6$ where R_6 is hydrogen, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-3} alkylamino, or di(C_{1-3} alkyl)amino; (b) phenyl or phenalkyl having from two to five R_5 substituents where each R_5, independently of the other(s), is halogen, cyano, trifluoromethyl, C_{2-3} alkanoyl, nitro, C_{1-3} alkyl, C_{1-3} alkoxy, carboxy, alkoxycarbonyl, trifluoromethoxy, acetamido, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, trifluoromethylsulfonyl or

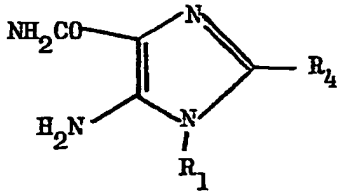
where R_5, X, and n are as defined above, provided that if the monosubstituent or one of the polysubstituents is halogen, C_{1-3} alkyl or C_{1-3} alkoxy, such atoms or groups are in positions other than those ortho to the positions of attachment of the phenyl to the imidazole or the alkyl that is in turn attached to the imidazole; or (c) phenacyl, pyridyl, pyridylmethyl, naphthyl, naphthylmethyl, quinolyl, or quinolylmethyl;

R_2 is amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, acetamido, acetimido, ureido, formamido, formimido or guanidino;

R_3 is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; and

R_4 is hydrogen, C_{1-3} alkyl, hydroxy, amino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, phenyl, cyano, C_{1-3} alkoxy, C_{2-3} alkanoyloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or C_{1-3} alkylsulfonyl.

2. A process for preparing a compound having the formula



comprising treating aminocyanoacetamide with an R_1-substituted amine in the presence of a compound of formula $(C_2H_5O)_3CR_6$ to produce the desired compound, R_6 being hydrogen, C_{1-3} alkyl, or phenyl and R_1 and R_4 being as defined in Claim 1.

3. A process as claimed in Claim 1 as applied to the preparation of a compound in which R_1 is monosubstituted phenyl or monosubstituted benzyl where the substituent is a trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl or phenylsulfonyl radical, a halo-substituted, methyl-

substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; a di- or trisubstituted phenyl or benzyl radical where the substituents are halogen, cyano, methyl, trifluoromethyl, phenoxy, benzoyl, phenylthio, phenylsulfinyl, phenylsulfonyl, or a halo-substituted, methyl-substituted or trifluoromethyl-substituted phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzoyl or phenylhydroxymethyl radical; provided that if the monosubstituent or one of the substituents is halogen, it is ortho to the position of attachment of the phenyl to the imidazole or to the methyl that is in turn attached to the imidazole;

R_2 is amino, C_{1-3} alkylamino or di(C_{1-3} alkyl)amino;
R_3 is carbamoyl and
R_4 is hydrogen.

4. A process as claimed in Claim 2 as applied to the preparation of a compound in which R_1 is as defined in Claim 3 and R_4 is hydrogen.

5. A process as claimed in Claim 1 or 2 as applied to the preparation of a compound in which R_1 is phenyl or benzyl radical having 2 or 3 halo, cyano, methyl, trifluoromethyl, halophenoxy, tolyoxy, trifluoromethylphenoxy, halophenylthio, tolylthio, trifluoromethylphenylthio, halophenylsulfinyl, tolysulfinyl, trifluoromethylphenylsulfinyl, halophenylsulfonyl, tolylsulfonyl, trifluoromethylphenylsulfonyl, halobenzoyl, methylbenzoyl, trifluoromethylbenzoyl, halophenyl-hydroxymethyl, methylphenyl-hydroxymethyl and/or trifluoromethylphenyl-hydroxymethyl substituents in the meta and/or para positions; and R_4 is hydrogen.

6. A process as claimed in Claim 1 or 2 as applied to the preparation of 5-amino-1-(3,4,5-trichlorobenzyl)imidazole-4-carboxamide.

7. A process as claimed in Claim 1 or 2 as applied to the prepration of 5-amino-1-[4-(4-chlorophenylthio)-3-chlorobenzyl]imidazole-4-carboxamide.

8. A process as claimed in Claim 1 or 2 as applied to the preparation of 5-amino-1-[4-(4-chlorophenoxy)-3-chlorobenzyl]imidazole-4-carboxamide.

9. A compound obtained by a process as claimed in any one of Claims 1 to 8 for use in administration to an animal for the purpose of preventing or treating coccidiosis.

10. A composition useful for the prevention and treatment of coccidiosis which comprises an inert carrier and a compound obtained by a process as claimed in any one of Claims 1 to 8.

European Patent Office

EUROPEAN SEARCH REPORT

0113570
Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 83307692.0

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	US - A - 4 265 900 (RASMUSSEN) * Claim 1 * --	1,2	C 07 D 233/88 C 07 D 233/60 C 07 D 401/04 C 07 D 401/06 A 61 K 31/415
A	EP - A1 - 0 028 834 (TAKEDA YAKUHIN K.K.K.) * Claim 1 * --	1,2	
A	CHEMICAL ABSTRACTS, vol. 96, no. 9, March 1, 1982, Columbus, Ohio, USA SUMITOMO CHEMICAL CO. "1-Triaryl-methylimidazoles" page 613, column 2, abstract-no. 68 990k & Jpn. Kokai Tokkyo Koho JP 81 79 671 --	1,2	
A	CHEMICAL ABSTRACTS, vol. 96, no. 17, April 26, 1982, Columbus, Ohio, USA TH. KAUFFMANN et al. "Hetero-cyclopolyaromatics XII" page 757, column 2, abstract-no. 142 826e & Chem. Ber. 1982 115(2), 452-8 --	1,2	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 233/00
C 07 D 401/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	20-03-1984	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503. 03.82

0113570
Application number

European Patent Office

EUROPEAN SEARCH REPORT

EP 83307692.0

D CUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 94, no. 13, March 30, 1981, Columbus, Ohio, USA PFIZER CORP. "Imidazole derivatives" page 747, column 1, abstract-no. 103 363r & Neth. Appl. 79 06 148 --	1,2	
A	CHEMICAL ABSTRACTS, vol. 97, no. 25, December 20, 1982, Columbus, Ohio, USA SANKYO KAGAKU K.K. "8-Quinolinesulfonyl derivatives" page 855, column 2, abstract-no. 216 195t & Jpn. Kokai Tokkyo Koho JP 82 116 067 ----	1,2	TECHNICAL FIELDS SEARCHED (Int. Cl.³)